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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/511,794
Filing Date: March 17, 2005
Appellant(s): GAVILONDO COWLEY ET AL.

Anna C. Chau
For Appellant

EXAMINER'S ANSWER

This is in response to the Appeal Brief filed 3/9/09 and the Response to Notification of Non-Compliant Appeal Brief to 37 CFR 41.37 filed 5/1/09 appealing from the Office action mailed 10/9/08.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

Applicants allege on p. 3, section III of the Appeal Brief:

"The subject matter of claims 32-36 and 39-43 were rejected in an Advisory Action dated May 20, 2008 and the subject matter of Claims 47-56 were rejected in an Office Action dated January 4, 2008. Claims 32-36, 39-43, and 47-56 were finally rejected in an Office Action dated October 9, 2008. Accordingly, claims 32-36, 39-43, and 47-56 are presently pending in the application and stand as finally rejected."

The examiner submits that Claims 32-36 and 39-42 have been finally rejected; once in the Office Action of 1/4/08, twice in the Advisory Action of 5/20/08 and thrice in the Office Action of 10/9/08.

The examiner submits that Claims 47-56 were first presented in the Response of 7/7/08 and once rejected in the Office Action of 10/9/08. The subject matter of Claims 47-56 corresponds to the same subject matter of Claims 32-36 and 39-43, respectively, from the Response of 10/5/07, and which was once rejected in the Office Action of

1/4/08 for Claims 32-36 and 39-42. The subject matter has been twice rejected but Claims 47-56 have not been twice rejected pursuant to MPEP 1204 and 35 U.S.C. 134.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the Response to Notification of Non-Compliant Appeal Brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The listing of evidence relied upon:

Tormo et al. (APMIS 97(12):1073-80 (1989))

Freyre et al. (J. Biotechnol. 76:157- 163 (2000))

Ayala et al. (Conf. On Plant-Made Pharmaceuticals 2005; Abstract))

Hollinger et al. (PNAS 90:6444-6448 (1993))

Appellant has relied upon a reference incorporated in the specification in their Arguments that was not previously cited during the prosecution proceeding:

Ayala et al. (Biotechniques 13: 790-799 (1992))

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 32-36, 39-42 and 47-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tormo et al. (APMIS 97(12):1073-80 (1989)) in view of Freyre et al. (J. Biotechnol. 76:157-163 (2000)) as evidenced by Ayala et al. (Conf. On Plant-Made Pharmaceuticals 2005; Abstract) and further in view of Hollinger et al. (PNAS 90:6444-6448 (1993)).

Claims 32-36 are interpreted as being drawn to a monomeric scFV consisting of amino acid sequence of SEQ ID NO:16 which binds to human CEA (Claim 32), further comprising a detectable agent (Claim 33), further where the detectable agent is a radioactive label (Claim 34) or a reporter molecule (Claim 35); and pharmaceutical composition comprising the sequence of SEQ ID NO:16 and a carrier (Claim 36).

Claims 39-42 are interpreted as being drawn to a divalent scFV consisting of amino acid sequence of SEQ ID NO:17 which binds to human CEA (Claim 39), further comprising a detectable agent (Claim 40), further where the detectable agent is a radioactive label (Claim 41) or a reporter molecule (Claim 42); and pharmaceutical composition comprising the sequence of SEQ ID NO:16 and a carrier (Claim 43).

Claims 47-51 are interpreted as being drawn to a monomeric scFV comprising amino acid sequence of SEQ ID NO:16 which binds to human CEA (Claim 47), further comprising a detectable agent (Claim 48), further where the detectable agent is a radioactive label (Claim 49) or a reporter molecule (Claim 50); and pharmaceutical composition comprising the sequence of SEQ ID NO:16 and a carrier (Claim 51).

Claims 52-56 are interpreted as being drawn to a divalent scFV comprising amino acid sequence of SEQ ID NO:17 which binds to human CEA (Claim 52), further

comprising a detectable agent (Claim 53), further where the detectable agent is a radioactive label (Claim 54) or a reporter molecule (Claim 55); and pharmaceutical composition comprising the sequence of SEQ ID NO:16 and a carrier (Claim 56).

The instant claimed monomeric scFv of SEQ ID NO:16 and the divalent scfv or diabody of SEQ ID NO:17 and pharmaceutical compositions comprising the same, were prima facie obvious at the time of the invention in view of Tormo, Freyre and Hollinger as evidenced by Ayala.

Tormo discloses the hybridoma CB/ior-CEA.1 which produces the murine Mab as being highly specific for human CEA with no cross-reaction with CEA-related molecules that shows no recognition of normal tissues, except for cells of the normal colon epithelium with polarized CEA expression. Applicants specification specifically teaches that the VH and VL domains comprising the scFv of SEQ ID NO:16 and 17 were derived from the antibody produced by the CB/ior-CEA.1 hybridoma of Tormo (see Example 1, p. 10, lines 35-39: "Total RNA from 10^6 cells of the mouse hybridoma CB/ior-CEA.1 (Tormo B. et al. APIMS. 97:1073-1080, 1989) was extracted with the TriPure™ reagent...".) ("The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property, which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1997). Tormo does not disclose Ab constructs such a

monomeric and diabody scFvs using the VH and VL domains from the parent antibody. Freyre as evidenced by Ayala and Hollinger rectifies this deficiency in its disclosure.

The scFv produced by Freyre et al. in 2000 using the VH and VL of CB/ior-CEA.1 was producible at high levels but reduced in affinity because numerous changes had been introduced into the VH/VL domains during PCR cloning as evidenced by Ayala. Ayala specifically teaches "A new scFv was constructed from newly amplified CB/ior-CEA.1 VH and VL genes, taking care to avoid the potential introduction of PCR mutations." And as evidenced by Ayala, Hollinger provided an alternative means for producing multivalent scFv forms and maintaining the integrity of the original VH and VL domain sequences of the parent antibody.

Hollinger discloses recombinant antibody fragments using variable domains encoded by genes from mouse hybridomas to make constructs for expressing scFv, bivalent and bispecific antibody fragments that have the advantages of retaining the antigen recognition of the parent antibody, being small in size, assembled in vivo and harvested directly from culture supernatant.

One skilled in the art would have been motivated to have combined the techniques of Tormo, Freyre and Hollinger as evidenced by Ayala to obtain an improved antibody fragment having the binding properties of the parent CB/ior-CEA.1 antibody and the advantages of being readily producible as a properly assembled and secreted antibody fragment by transfected cells in vitro or in vivo, and been reasonably assured of success in producing such based on the disclosures of Tomoro, Freyre as evidenced by Ayala and Hollinger. The Tormo CEA antibody was highly selective and non-

crossreactive for purposes of using such an antibody in targeted diagnostics or therapeutics for CEA-expressing tumors, and because obtaining smaller sized Ab fragments was more desirable for retaining antigen binding and for tumor penetration, one skilled in the art would have been motivated to have obtained scFv from the CB/ior-CEA.1 parent antibody based on Freyre, and because Freyre's scFv was already established at the time of the invention to retain antigen specificity albeit reduced affinity compared with the parent Ab as evidenced by Ayala, one would have been further motivated to have obtained an scFv or diabody which possessed reproducible and approximate binding properties to the parent Mab based on the disclosure of Hollinger for producing scFvs replicating the binding properties of the respective parent antibody. Taken together, one skilled in the art would have been reasonably assured of success in producing the instant claimed CEA antibody embodiments based on the disclosures of Tormo, Freyre as evidenced by Ayala and Hollinger because all the materials and reagents were available for producing the recombinant CEA Abs, and as evidenced by Freyre the importance of VH and VL sequence fidelity in generating a scFv with high affinity binding was established and Hollinger provided an alternative method to for cloning VH and VL domains from a parent Mab into a scFv or diabody structure in order to produce a smaller sized but high affinity antibody variant of the parental Mab. Further all of the reference appreciated obtaining small sized fragments for pharmaceutical applications.

(10) Response to Argument

Appellant's summary arguments on pp. 7-14 of the brief are further summarized as follows:

On p. 8 Appellant's allege:

> "The cited references, alone or in combination, fail to disclose or suggest any amino acid sequence, much less the specific amino acid sequences as required by claims 32-36, 39-43, and 47-56. In fact, the examiner provided no evidence establishing that any of the cited references taught or suggested any amino acid sequence even remotely related to the claimed sequences."

Response to Arguments

The examiner respectfully submits whereas in the instant case, Appellant's own specification teaches the same antibody, CB-CEA-1, as disclosed in Tormo and further incorporates by reference the actual Tomoro reference as the source for the CB-CEA-1 antibody, that the VH and VL domains of the instant claimed scfv antibody are necessarily inherent to Tomoro's antibody. Both of the VH and VL domains of the monomeric and divalent scFvs are obtained from and are the same as the VH and VL domains from the parent monoclonal produced by Tomoro's CB/ior-CEA.1 hybridoma. The cited references provide motivation to produce small sized antibody fragments such as scFvs, and the cited references would allow the ordinary artisan to be reasonably assured of success in producing scFvs having high fidelity binding to the antigen using a linker known in the art and the cloned VH and VL domains based on the PCR techniques of Freye as evidenced by Ayala and further in view of Hollinger.

On p. 9, Appellant's allege:

"For example, the claimed monomeric and divalent scFv antibody fragments have important differences in the amino acid sequences of the VH and VL domains when compared with prior art scFv fragments. See specification p. 3, lines 29-35. There are differences with at least sixteen amino acids in the VH domains and with at least three amino acids in the VL domains between the claimed scFv fragments and those disclosed in Ayala et al. (Biotechniques 13: 790-799, 1992). id. Ayala (I 992) was cited in the Freyre reference on page 158: "...we have developed several scFv gene constructions that have been expressed as biologically active antibody fragments in the periplasm of Escherichia coli (Ayala et al., 1992)")."

Response to Arguments

The examiner respectfully submits that Freyre as evidenced by Ayala in view of Hollinger established that the VH and VL domains from Tomoro's CB/ior-CEA.1 antibody could be cloned, used in the construction of a scFv construct and measured for its binding affinity against the parent antibody VH/VL domains found in a Fab fragment. Freyre as evidenced by Ayala in view of Hollinger provided motivation to avoid introducing PCR mutations into the VH and VL domains of Tomoro's CB/ior-CEA.1 antibody in order to avoid the significantly decreased binding affinity for the scfv to CEA. Ayala teaches:

> A new scFv was constructed from newly amplified CB/ior-CEA.1 VH and VL genes, *taking care to avoid the potential introduction of PCR mutations*. We also developed a multivalent scFv with these variable regions, using a five-amino acid linker during its assembly, as suggested by Holliger, P., et. al, 1993), and with a c-myc derived peptide and polyhistidine tag attached in the C-terminal.

The combined reference disclosures teach maintaining the sequence integrity and identity of the VH and VL domains in the scfv derived from Tomoro's CB/ior-CEA.1 antibody in order to avoid reducing the affinity of the scfv for CEA.

On pp. 10-11, Applicants allege:

> "...the claimed scFv antibody fragments are not "inherent" based on the disclosure of the monoclonal antibody in Tormo, and they are not structurally similar to the compositions disclosed in the references."
>
> "...the examiner is in error because the examiner failed to take into consideration all of the elements of the pending claims. The examiner failed to consider the specific amino acid sequence elements of the pending claims, and the examiner failed to consider the structural

> differences between the claimed scFv antibody fragments and the compositions disclosed in the references. Accordingly, the examiner failed to establish a prima facie case of obviousness..."

Response to Arguments

The examiner respectfully submits that the instant claimed scfv and divalent scfv comprises VH and VL domains derived from Tomoro's CB-CEA-1 antibody as incorporated by reference in the specification at p. 3, lines 4-6 and in Example 1, at p. 10, lines 35-39. The linker comprising the scfv and divalent scfv is taught by Ayala as being derived from Hollinger and Applicants have not shown the linker of Ayala in view of Hollinger differs from the linker of the claimed scfvs. Applicants have not articulated which of the specific elements of the claims are not explicitly or implicitly taught directly or by reference amongst the cited references of record, and amongst which share common authorship with Inventor Gavilondo of the instant invention.

On p. 12-13, Applicants allege:

> CEA antibodies are not predictable because "scfv fragments developed by previous investigators (e.g., Freyre (2000) and Ayala (1992)), failed to exhibit a high affinity for the target antigen CEA and a proper biodistribution in test animals. See specification at p. 2, lines 29-40, and Ayala (2005), first paragraph, which states that the affinity of the scFv disclosed in Freyre "was shown to be 200 times lower than that of the Fab obtained by enzyme digestion of the original Mab" (citations omitted)."

Response to Arguments

The examiner respectfully resubmits that Freyre as evidenced by Ayala provided motivation to avoid introducing PCR mutations into the VH and VL domains of Tomoro's

CB/ior-CEA.1 antibody in order to avoid the significantly decreased binding affinity for the scfv to CEA. Ayala teaches:

> "...the affinity of F3 for immobilized antigen in Biacore was shown to be 200 times lower than that of the Fab obtained by enzyme digestion of the original Mab...A new scFv was constructed from newly amplified CB/ior-CEA.1 VH and VL genes, *taking care to avoid the potential introduction of PCR mutations*."

On p. 13, Applicants allege:

> "As Appellant explained earlier, Ayala (2005) discloses the creation of a scFv antibody fragment in which measures were taken to avoid potential introduction of PCR mutations. However, Ayala does not state that the reduced antigen affinity exhibited by the scFv of Freyre was due to PCR mutations. In fact, Ayala does not disclose or suggest any reason for the reduced affinity for CEA observed in Freyre."

Response to Arguments

The examiner respectfully submits that Ayala specifically teaches that Freyre's Ior-CEA-1-derived F3 antibody had reduced affinity for CEA because of mutations introduced into the variable domains during PCR cloning where Ayala teaches:

> "A single chain Fv (scFv) antibody fragment (denominated F3) of the CB/ior-CEA.1 Mab was obtained by PCR amplification and assembly of variable regions and successfully expressed in E. coli and in the yeast Pichia pastoris (Freyre, F.M. el. al., 2002). However, the affinity of F3 for the immobilized antigen in Biacore was shown to be 200 times lower than that of the Fab obtained by enzyme digestion of the original Mab (Perez Let al., 1996)."

On pp. 13-14, Applicants allege:

> "...the combined cited references are devoid of any identification or prediction of the at least sixteen amino acid differences in the VH domains and the at least three amino acids in the VL domains between the claimed scFv fragments

> and those of the prior art. See specification p. 3, lines 29-35. That is, nothing in the combination of cited references identified or predicted any sequence variations to make for correcting any alleged PCR mutations in order to arrive at the claimed invention."

Response to Arguments

The examiner respectfully submits that Appellant's have not made reference to the prior art anti-CEA antibody of Ayala et al. (Biotechniques 13: 790-799 (1992)) described on p. 3 at lines 29-35 of the specification anywhere in the prosecution history and prior to filing their Appeal Brief.

Nevertheless, the specification teaches by reference to Ayala et al. (Biotechniques 13: 790-799 (1992)) where PCR cloning mutations were introduced into the VH and VL domains of the CB-ior-CEA-1 antibody of Tomoro. Accordingly, it is the examiner's position that the specification through incorporation to Ayala is dispositive to Appellant's argument because the specification (and Ayala) teach away from these and any PCR mutations in the variable domains in order to obtain a scfv with properties similar in behavior to the parent Mab CB/ior-CEA-1. In fact, the specification on p. 3, lines 39-41 teaches that the scfvs of the invention having greater fidelity to the VH and VL domains of Tomoro's original CB/ior-CEA-1 have a very similar behavior to the parent antibody.

The examiner maintains that the CB/ior-CEA-1 antibody of Tomoro was well known at the time of the invention, and the methods for making a scfv comprising the VH and VL and the linker of the instant claims were taught by Freyre as evidenced by Ayala and Hollinger, and further that Ayala taught away from introducing PCR mutations

in the VH and VL domains in order to obtain a scfv or dimeric scfv having similar properties to the parent antibody of Tomoro.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For all the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted

/Lynn Bristol/
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